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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
COOK, LISA V	
ART UNIT	PAPER NUMBER
1641	10

DATE MAILED: 02/12/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/624,131	KAPUR ET AL.	
	Examiner	Art Unit	
	Lisa V. Cook	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 September 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-17* is/are pending in the application.

4a) Of the above claim(s) *1-10* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *11-17* is/are rejected.

7)☒ Claim(s) *13 and 14* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1)☐ Notice of References Cited (PTO-892)
2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3)☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 7 .
4)☐ Interview Summary (PTO-413) Paper No(s). _____ .
5)☐ Notice of Informal Patent Application (PTO-152)
6)☐ Other:

DETAILED ACTION

Amendment Entry

1. Applicants' response to the Office Action mailed 25 March 2002 (paper #9 filed 9/24/02) is acknowledged. In amendment-A filed therein the specification was amended, while new claims 15-17 were added. Currently, claims 1-14 are subject to Restriction and Election Requirement. Claims 1-10 have been withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as claims drawn to a non-elected invention. Claims 11-17 are under examination.

OBJECTIONS WITHDRAWN

Priority

2. An application in which the benefits of an earlier application are desired must contain a specific reference to the prior application(s) in the first sentence of the specification (37 CFR 1.78). The cross-reference section should be updated to include patent # 6,103,479. (i.e. 08/865,341, filed on May 29, 1997, now Patent #6,103,479.

Applicant has amended the first line of the specification to include recent Patent Numbers. Therein obviating the rejection.

Information Disclosure Statement

3. The information disclosure statement filed 3/22/02 in paper #7 has been considered as to the merits before Final Action. The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609 A(1) states, "the list may not be incorporated into the specification but must be submitted in a separate paper."

Therefore, unless the examiner on form PTO-892 or applicant on PTO-1449 has cited the references they have not been considered.

Specification

4. *Applicant's have corrected the objections to the specification. Accordingly the objection is withdrawn.*

OBJECTIONS MAINTAINED

Drawings

5. The drawings in this application are objected to by the Draftsperson as informal. Any drawing corrections requested, but not made in the prior applications should be repeated in this application if such changes are still desired. If the drawings were changed and approved during the prosecution of the prior applications, a petition may be filed under 37 CFR 1.182 requesting the transfer of such drawings provided the parent application has been abandoned. However, a copy of the drawings as originally filed must be included in the 37 CFR 1.60 application papers to indicate the original content. *Applicants will file a set of formal drawings under separate cover. The objection is maintained.*

Claim Objections

6. Claims 13 and 14 are objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim cannot depend from any other multiple dependent claim. See MPEP § 608.01(n). Claim 13 is dependent on both claims 11 and 12, while claim 14 is dependent on the multiple dependent claim 13. Accordingly, claims 13 and 14 have not been further treated on the merits. *Applicants have not addressed the following objection, it is maintained.*

REJECTIONS WITHDRAWN

Claim Rejections

7. With respect to the claim rejection under 35 U.S.C. 103, Applicant argues that the references do not teach or suggest all the claimed limitations. Applicant's arguments have been fully considered and found persuasive. The following rejection of claims 11 and 12 are rejected under 35 U.S.C. 103(a) as being unpatentable Taylor et al. (Optical Diagnostics of Living Cells and Biofluids, Vol. 2678, 1996, pages 15-27) or Taylor et al. (American Scientist, 80:322-335, 1992) in view of Hendzel et al. (Chromosoma, 1997, 106:348-360) is withdrawn.

NEW GROUNDS OF REJECTION NECESSITAED BY AMENDMENT

Double Patenting

8. Double patenting obviousness-type rejection:

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

9. Claims 11-17 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-20 of Application 09/513,783 now U.S. Patent No. 6,416,959.

Although the conflicting claims are not identical, they are not patentably distinct from each other because both inventions are drawn to cell analysis procedures employing the same method wherein multiple luminescent-labeled reporter molecules are used to label the protein of interest, the cell, and location.

Specifically in claim 3 multiple cells are analyzed in an array of locations (column 321), while claim 17 provides first and second array locations (column 324), wherein the second array can comprise either the same or a different cell type as the first array (column 326).

US Patent #6,416,959 differs from the instant invention in not specifically reciting that the different cell types being analyzed are derived from different organ types. However, the type of cell utilized in the analysis is considered mere optimization of the inventive method. It would have been obvious to one having ordinary skill in the art at the time the invention was made to employ any number of cells or cells derived from different organs, since it has been held that the provision of adjustability, where needed, involves only routine skill in the art. *In re Stevens*, 101 USPQ 284 (CCPA 1954).

REJECTIONS MAINTAINED

Claim Rejections - 35 USC § 103

11. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negative by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

I. Claims 11 and 12 are rejected under 35 U.S.C. 103(a) as being unpatentable Taylor et al. (Optical Diagnostics of Living Cells and Biofluids, Vol. 2678, 1996, pages 15-27) or Taylor et al. (American Scientist, 80:322-335, 1992) in view of Hendzel et al. (Chromosoma, 1997, 106:348-360).

Taylor et al. (Optical Diagnostics of Living Cells and Biofluids) teach new technologies used in conjunction with light microscopy to measure events in living cells via an automated method. The new automated methodology involves cell imaging and scanning techniques that are extrapolated to identify signal as digital data subsets for further analysis (multidimensional image data). See page 16, 3rd and 4th paragraphs.

Taylor et al. (American Scientist) teach new technologies used in conjunction with light microscopy to measure events in living cells. One major advance of the new methodology is found in the use of computers for digital processing and analysis of images.

Another improvement is seen in the development and use of fluorescent dyes, which can be attached to specific molecular structures thereby revealing the location of those structures in the cells. Dye molecules can also be designed so that their fluorescence is controlled by specific physiological changes; thus they indicate what is happening in the cells, as well as when and where (page 322, column 3, 1st paragraph). Taylor et. al. teach modified multi-mode light-microscope workstations that incorporate multiple electronic detectors and provide computer control of all major microscope functions. Images are converted to a digital form that can be read and manipulated by the computer (pages 324 & 325).

Taylor et. al. teach indicators that reveal where a marker has gone in the cell and what conditions exist in that area, as well as the use of more than one tagging molecule with one or more suitably chosen fluorescent labels to learn whether or not the molecules are close to each other in the cell. When one label is stimulated to fluorescence, it can transfer part of its energy to the second label molecule, leading to fluorescence at another wavelength (page 328, figure 8). Thus meeting the limitation of dual luminescent reporter wherein one is a detector and the other is a classifier. Taylor et. al. also teach the measuring of changes in excitation or emission spectrum of an indicator using a mode of microscopy known as ratio imaging which relies on digital post-processing. The method is exemplified by the measurement of calcium concentration (applicant's toxin).

Two images are recorded, one in the calcium-sensitive part of the spectrum and the other at a calcium-independent wavelength, then all the pixel intensities of the Ca2+ sensitive images are divided by those of the Ca2+ independent image. The resulting ratio image is normalized for variations in the optical path length, in the volume accessible to the calcium probe and in the concentration of the probe, and provides a map of the intercellular concentration of free calcium ions.

Taylor et al. and Taylor et al. differ from the instant invention in failing to teach multiple cell analysis comprising two or three cell types with respect to toxin (test compound exposure).

However, Hendzel et al. teach the relationship between H3 phosphorylation and mitotic chromosome condensation in mammalian cells. The precise spatial and temporal correlation of chromatin is evaluated. (abstract and page 349 –1st column) Nuclear mask or nuclear staining images are compared and correlated to the various phases of mitosis (mitotic index). See page 353 Progression of H3. Dual staining procedures to evaluate location and mitotic state are described (anti-phosphorylated H3 "red" and ACA autoimmune "green" sera). See page 354, 2nd column. The method is evaluated with respect to the L929(murine), C6 glioma (rat), HeLa(human), SAOS-2(human), and Indian muntjac cell lines. See page 352, 2nd column, 1st paragraph, last sentence and page 354, 2nd column 1st paragraph, last sentence.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to measure multiple cell types as taught by Hendzel et al. in the methods Taylor et al. and Taylor et al., to perform toxin detection and organ localization, because Hendzel et al. taught that several cells could be analyzed via digital imaging (Vaytek MicroTome Software) allowing

for the removal of out of focus information (adjacent sections), point spread functions, rescaling, and color co-localization images. See pages 350-351.

One having ordinary skill in the art would have been motivated to do this to acquire the enhanced sensitivity and ability to reduce background fluorescence while providing more data sets for analysis, wherein accurate and precise detection is rapidly available.

Response to Argument

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., dual luminescent reporter wherein one is a detector and classifier is not recited in claims 11 and 12) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5

USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, applicant argues that the mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination.

In response it is noted that it would have been obvious to one of ordinary skill in the art at the time the invention was made to measure multiple cell types as taught by Hendzel et al. in the methods Taylor et al. and Taylor et al., to perform toxin detection and organ localization, because Hendzel et al. taught that several cells could be analyzed via digital imaging (Vaytek MicroTome Software) allowing for the removal of out of focus information (adjacent sections), point spread functions, rescaling, and color co-localization images. See pages 350-351.

One having ordinary skill in the art would have been motivated to do this to acquire the enhanced sensitivity and ability to reduce background fluorescence while providing more data sets for analysis, wherein accurate and precise detection is rapidly available.

Applicant contends that the references are not directed to toxin detection. However, the method of both Taylor et al. references exemplify the measurement of calcium concentrations (applicant's toxin). In large quantities such concentrations are harmful to the cell/toxic and the instant claims do not specifically recite particular toxins, therein the cited art reads on claims 11 and 12.

12. For reasons aforementioned, no claims are allowed.

13. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Remarks

14. Prior art made of record and not relied upon is considered pertinent to the applicant's disclosure:

A. Price et al. (USP# 5,790,710) disclose an autofocusing system for obtaining measurements of fluorescent stained cellular components by scanning multiple microscope fields.

B. Harpold et al. (USP# 5,436,128) teach methods for detecting and evaluating intracellular transduction on extracellular signals.

15. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform to the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The Group 1641 Fax number is (703) 308-4242, which is able to receive transmissions 24 hours/day, 7 days/week.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lisa V. Cook whose telephone number is (703) 305-0808. The examiner can normally be reached on Monday-Friday from 8:00 AM - 4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le, can be reached on (703) 305-3399.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Lisa V. Cook 1/27/03

Lisa V. Cook
CM1-7B17
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02/07/03